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Theranostics an Emerging Paradigm- a Review

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Abstract: *Nanomedicine is the utilization of knowledge and tools of nanotechnology in the field of medicine. Theranostics is one of the new emerging fields in the branch of nanomedicine. Theranostics combines therapy and diagnostics. Theranostics focuses on the integration of information from a diverse set of biomarkers to create pharmaceutical formulations for a targeted subpopulation where the drug can display greater therapeutic efficacy and less toxicity. Nanoparticles are available in various forms which include Quantum dots, dendrimers, gold nanoparticles, liposomes, magnetic nanoparticles, carbon nanotubes. The unique size dependent electronic, optical, thermal, mechanical properties of nanomaterials are the properties that make them to use in the field of medicines. The high surface area: volume ratio renders nanoparticle with the ability to function with the surface moieties that can be used to target specific sites, sequester proteins or even silence a gene inside the living cell. Theranostics composed of carrier agents that are incorporated with plasmid, nucleic acids and proteins that help to diagnose with the help of nanoparticles to target the peptides, antibodies, vitamins. Nanoparticles had various applications in the field of medicine and have more advantage than the conventional therapies. It plays a key role in the treatment of cancer therapeutics in targeting the cancer cells and in biomarker discovery. The simultaneous imaging and therapy of nanoparticles with multifunctional properties provide opportunities in the field of medicine. This review emphasizes the forms of theranostic nanomedicine and its advantages over the conventional therapies.*

Keywords: *Theranostics, Nanoparticles, Cancer Therapy, Diagnostics.*

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I. Introduction

Nanotechnology is the multidisciplinary approach incorporating physical, chemical and beneficial effects on the living matter at nanoscale. Nanomedicine is the utilization of knowledge and tools of nanotechnology in the field of medicine. Now a day, molecular technology plays a key role in the branch of medicine and dentistry. They enable early detection, prevention, treatment and follow up of diseases.[1] Theranostics is one of the new emerging fields in the branch of nanomedicine. The new branch of "Theranostic" was formulated by Funkhouser in 2002.[2] Theranostics - portmanteau of therapeutics and diagnostics Portmanteau means a combination of two (or more) words into one new word. Theranostics combines therapy and diagnostics. The term "theranostics" was coined to explain the developments in science to establish more specific and individualized therapies for various pathologies, and to bring about a union of diagnostic and

therapeutic applications into a single agent thus leading to a promising therapeutic paradigm involving diagnosis, drug delivery and monitoring of treatment response.[3]

Theranostics locus on the assimilation of information from a various set of biomarkers to create pharmaceutical formulations for population groups where the drug can provide greater treatment efficiency and lesser toxicity.[4]From the biomarker discovery nanomedicine helps in delivering the theranostic materials as diagnostic sensors and therapeutic formulations.[1]

Theranostics helps in the management of various diseases and cancer therapeutics. Cancer therapy greatly relies on conventional radiotherapy and chemotherapy in which anti cancer drugs are taken by the cancer cells at high proliferative rate. The drawbacks of conventional therapy is that the normal cells also get affected by chemotherapeutic action resulting in several side effects.[5]

The rationale for this novel discovery in nanomedicine is that diseases, such as cancers, are extremely heterogeneous, and all necessary treatments are effective for only few patient subpopulations and at different stages of disease development. Targeting approaches can differ much to suit the desired target.[6]

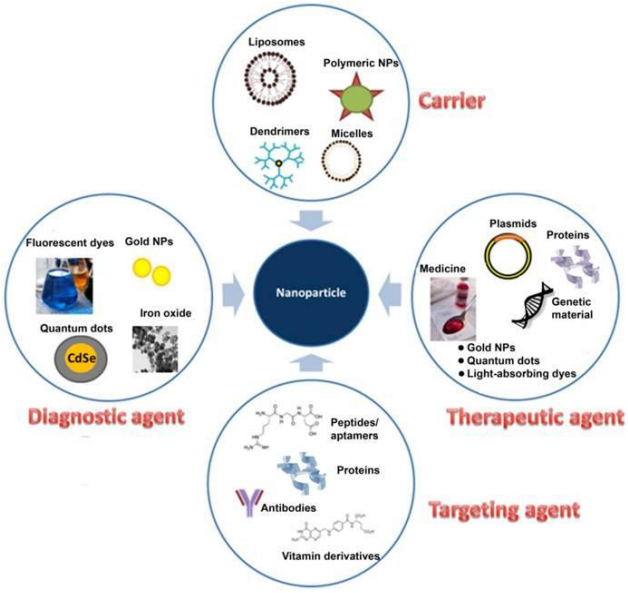
Uniqueness of Nanoparticles

On December 29th 1959, late Nobel physicist Richard P Feynman gave a lecture titled "there is plenty of room at the bottom," he proposed that there is a possibility to made a machine at nanolevel, this leads to the development of new idea which become a reality today in the recent research perspectives in the field of medicine.[1]

Nanomedicine is the application of nanotechnology in the field of medicine. The prefix nano comes from the Greek word nanos, or "dwarf" and means one-billionth of any material and the materials that are smaller than 100 nanometers (nm) in one of the dimension. The uniqueness of nanoparticles is its smaller size which avoid uptake by the Reticulo-endothelial system and large enough to avoid clearance level in the renal system and leakage from blood vessels except at target tissue e.g., tumour cells where blood vessels are leaky in our body.[1]

Figure 1: Components of nanoparticle based drug delivery system

The Best and First Theranostic Agent



In 19th century it was the Iodine 131 identified as best theranostic agent in the treatment of thyrotoxicosis. This isotope when radiated to the patient it not only identify the benign condition but also helps in the treatment of thyroid cancer.[7]

The beta emitting radioactive iodine when administered they selectively kill or harm the thyroid cancer cells and specifically deposit more iodine and the cells can be visualized in gamma camera using gamma rays emitted from Iodine 131. They also helps in identifying the recurrence at an earlier stage depend upon the serum thyroglobulin measurement or radioiodine imaging by removing residual normal thyroid tissues.[8]

Pharmacogenetics

Pharmacogenetics is the science that deals about the individual variations in DNA sequences and responses to treatment interventions by the use of biomarker. This genotyping approach helps in tailoring drug therapy with advantages like reduction in time and cost and increase in success rates. The field of

pharmacogenomics extends to involve variations in RNA and proteins also that may have important role in treatment. Genetics play an important role in theranostics and promoted by human genome project to identify the variation in genes.[3] The components of nanoparticles includes diagnostic agent, Therapeutic agent, Targeting agent and Carrier (Figure 1)

Quantum Dots

Quantum dots are the nano crystals discovered by Dr. Bawendi.[1] They have advanced the field of diagnostics and nano therapeutics by their high surface volume ratio and act as a nano scaffold for theranostic modalities.[9]

The photon of proper energy when impinges the semiconductor, excitation takes place and it generates an electron-hole pair that is weekly bound by coulomb forces. The same property is utilized by the quantum dots in which the dimensions are less than the Bohr exciton radius and the energy levels are quantized. This effect leads to superior optical properties of quantum dots with narrow, symmetric and broad excitation spectra with high fluorescent stability.[9]

The advantage of quantum dots is that the variously sized nanocrystals can be excited and preserving the narrow emission of individual wavelength. They also have the ability to incorporate different biomarkers to target the tissues at the same time. The problem faced in the use of quantum dots were the instability and water dispersability, but this was resolved by using various surface coatings like include antibodies, peptides, and small-molecule drugs/inhibitors which increases the stability of the quantum dots and also helps in incorporating tumor-targeting ligands for tumor identification.[10]

It can also bind to the antibody present on the surface of the target cell when stimulated by UV light and produce the reactive oxygen species thereby destructing the target cells.[11]

Dendrimers

Dendrimers are macromolecular structures that consists of a series of branches around an inner core that can encapsulate therapeutic agents within their core and also incorporated with cell identification tags, fluorescent dyes, enzymes and other molecules onto the "hooks'' present on their surface.[1] The advantage of dendrimers is their exclusive branching point that is available for conjugation to multiple entities including targeting proteins, treatment moieties, and even apoptosis factor ligands.[10]

The two main types of dendritic polymers, dendrimers are perfectly branched and monodisperse and hyper branched polymers. They have the properties, such as biodegradability, biocompatibility, stimuli-responsiveness and self-assembly ability, which are the key points for theranostic applications.[12]

Biomaterials like dendrimers with on-demand responsive properties to release cargoes will lead to significant use in vitro and in vivo therapeutic efficacy, mainly in the cancer therapy. For in vivo tumor environment various stimuli are used to stimulate the responsive behaviors like extracellular pH, the concentration of glutathione to achieve responsive properties, such as light, magnetic field, electrical field, temperature, ultrasounds. These stimuli-responsive dendritic polymers incorporated with anticancer drugs will respond to corresponding stimuli fastly and thus release the drugs with much therapeutic efficacy and minimal side effect.[12]

They can be used in the different field of theranostics like chemotherapeutic theranostics, biotherapeutic theranostics, phototherapeutic theranostic, radio therapeutic theranostics and combined therapeutic theranostics.[12]

Liposomes

Liposomes invented by Alec D Bangham at the Babraham Institute in the University of Cambridge in 1960. It is made up of single or multiple concentric lipid bilayers incorporating an aqueous compartment. The first formulations were composed only of natural lipids; at present they added natural and synthetic lipids, surfactants. They have the capability to entrap both lipophilic and hydrophilic agents, in the lipid membrane and in the aqueous core, respectively.[13]

The liposomes incorporated with the lipid bilayer protect it against naturally occurring phenomena, like enzymatic degradation and immunologic, chemical inactivation. Thus liposomes prevent a drug from being metabolized before reaching target tissues. They also minimize the exposure of normal tissue to the drugs during the time of circulation in the blood. It reduces the adverse effect of free form of liposomes.[13] The liposome-based formulations for gene therapy, such as synthetic cationic liposomal-DNA called lipoplexes, have greater potential to utilize in oral cancer treatment.[14]

Magnetic Nanoparticles

Magnetic nanoparticles are widely used for nano particle based drug delivery systems. They can be made in different sizes and can be surface coated in order to carry the molecules. Nanoparticles are used in

transporting various substances like antimicrobial molecules, genes, proteins and anti cancer drugs. Nanoparticles have dual function, to protect the therapeutic agent from degradation and then help to deliver it to cancer cells. Magnetic nanoparticles technology also attracts nanoparticles near the tumour and increases gene transfer into cells. This technique is called magnetofection. The disadvantage of this approach is that they are not applicable for non-accessible tumours.[15]

Fullerenes and Nanotubes

Fullerenes composed are also known as 'bucky balls' available in the shape of hollow or ellipsoid pattern. Fullerenes have the potential to induce the host immune response and formation of fullerene specific antibodies. Nanotubes are the tube like structures available as carbon nanotube, inorganic nanotube, DNA nanotube, membrane nanotube etc. They also used to transport DNA across cell membrane during gene therapy.[16]

Gold Nanoparticles

Gold nanoparticles (AuNPs) have been used as drug carriers, photo thermal converters, radiosensitizers, and imaging probes in cancer diagnosis and therapy.[17]

AuNPs are distinguished into nanospheres, nanorods, nanoshells, nanocages, and surface- enhanced Raman scattering (SERS) nanoparticles, based on their size, shape, and physicochemical properties. AuNPs have many features that make them unique in cancer theranostics. AuNPS are biocompatible and can be readily functionalized by attaching a variety of molecules to their surfaces. Gold nanoparticles attach to the drug delivery system easily because of their versatile nature.[17]

AuNP can act as efficient drug carriers. Targeted drug delivery enhances the tumor's uptake of the drug and reduces the availability of the drug to the healthy organs and increases the drug's therapeutic window. It was also reviewed that to 60% of a doxorubicin payload could be loaded onto hollow gold nanospheres. They were adsorbed to the surfaces of the hollow gold nanospheres via electrostatic attraction.[17]

Microbubbles as Cancer Theranostics

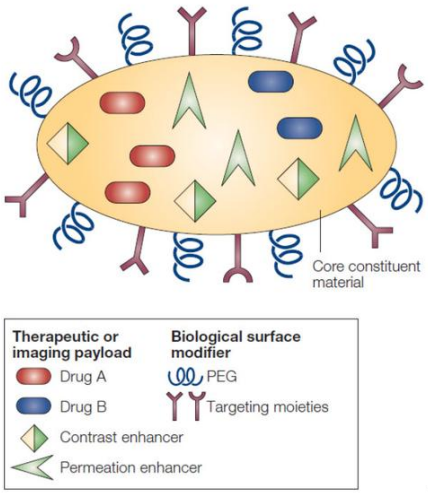
Microbubbles are smaller in size and used in various fields of science. Conventional micro bubbles of micron diameter cannot escape from the blood pool, the initial target is the blood vasculature. Ligands to VEGF1 can be attached to micro bubbles. It helps to identify the tumour neovascularization. They temporarily open the blood vessels and conduct the impulses for the endothelial barrier for a while and helps in therapeutic and diagnostic purposes.[18]

Components of Nanoparticle Based Drug Delivery System

Theranostics composed of carrier agents like liposomes, dendrimers, polymeric nanoparticles, carbon nanotubes incorporated with plasmid, nucleic acids and proteins helps to diagnose with the help of quantum dots, gold nanoshells to target the peptides, antibodies, vitamins.[19]

The nanoparticles are conjugated into the drug payload containing a Y shaped ligand deliver the diagnostic and therapeutic agent into the surface of tumor cells. They undergo enhanced permeability and retention (Figure 2). The tumor cell also develops its vasculature than the normal cells thereby allowing the drug to pass through the interstitial space.[1]

Figure 2: Mechanism of drug delivery system in cancer theranostics



Applications and advantages of theranostics in Oral Pathology

Today's Biomarker Tomorrows Theranostics

Theranostics helps in the identification of biomarker that help the medical practitioners to treat the individual patients depend upon their biomarker profile thereby enhancing the bioavailability and reducing the side effects. The ongoing research going on in this particular field to develop this field of drug development.[1]

Chemotherapy

The one of the most common drug used for the conventional treatment of cancer is cisplatin. The various researches proves that hydrophilic poly (ethylene glycol) shell layer enables the particles to circulate for long time in the blood compartment which will facilitate its preferential accumulation in the tumor tissues.[20]

Curcumin NPs (Cur-NPs) induce cell apoptosis in CAL27- cisplatin resistance human oral cancer cells (CAR cells) and inhibit cell growth but possess little cytotoxicity to normal human gingival fibroblasts cells and normal human oral keratinocyte cells. The findings suggest that Cur- NPs trigger apoptotic cell death through regulating the function of MDR1 and the production of reactive oxygen species, and the activation of caspase-9 and caspase - 3 connected to intrinsic signaling pathway is the major pharmacologic action of Cur-NPs. Cur-NPs show promise for development as a novel medicine against cisplatin resistant human oral cancer.[21]

Biotherapy

The gene therapy is method of transferring genetic materials into specific cells to treat diseases. These genes act therapeutically by regulating the amount of proteins, adjust the gene expression and generate cytotoxic proteins. Non viral gene vectors helps in efficient loading of genes in the region but they have certain limitations like they remain unstable when circulate in the blood stream and cell specific targeting system needed for the effective process. So drug delivery can be mediated by nanoparticle based theranostic reagents.[12]

Phototherapy

Nanoparticles help in delivering the photo sensitizers to the site of lesion and induce cell apoptosis. They also promote excitation and auto-fluorescence to endow with theranostic modality. [12]

Photo Thermal Therapy

Photodynamic therapy (PDT) achieves its therapeutic effects through the different mechanism from drug and gene delivery. It also helps in delivering an anticancer drug or protein or altering gene expression, nanotheranostic particles used for this purpose destroy their targets. This is a minimally invasive technique that kills target cancer cells in the presence of oxygen by the release of reactive oxygen species upon light activation of a photosensitizer. This kills the cancer cells through direct cellular damage, vascular shutdown, and induction of the host immune response to oppose the target cells.[22]

Application of Cytology Based Theranostics in Oral Squamous Cell Carcinoma

It was found in the study that theranostics along with oral brush cytology proved to the best way in profiling the biomarker in oral squamous cell carcinoma diagnosis. The prognostic significance of the epidermal growth factor receptor (EGFR) family and the angiogenic pathway in oral squamous cell carcinoma are also correlated with help of the targeted therpy.[23]

Immune Response

Nanoparticles containing drug molecules called interleukins are attached to certain immune cells (T-cells). Nanoparticles will release the T-cells along with the drugs and the T cells are reproduced in it. It results in destroying the cancer cells. Combining the effects of magnetic nanoparticles that attach to cancer cells in the blood stream may allow the cancer cells to be removed before they establish new tumours. Polymer nanoparticles to deliver a molecule called JSI-124 to cancer tumours. This molecule suppresses the ability of the cancer cells to affect the immune system and reduces the growth of cancer tumours. [24]

Cancer Therapy

Molecular diagnostics by imaging used to locate the tumour to guide target-specific therapy. Monoclonal antibodies reduce the systemic toxicity and provide the synergistic effect with the nanomedicine formulation. Nanoparticles which emit light of different colours could helps in the identification of different markers. Nanoparticles can be developed in the way that is naturally biodegradable and they can be eliminated easily from the body by natural metabolism.[12]

MMPs (matrix metalloproteinases) are the main prognosticators for metastasis and invasion potential of aggressive malignancies like oral squamous cell carcinoma. The property of down- regulation of MMP- 2

acquired in group treated with dual action DOX- MTX- NPs (Doxorubicin- Methotrexate loaded- NPs) whilst such a potential never reported for free DOX.

The MMP- 2 expression in OSCC, DOX- MTX- NP inhibit effectively and specifically progression and invasion of tumoral cells without affecting the normal tissues. However, further investigations acquire to clarify the underlying mechanism of action and its further therapeutic potentials in different types of cancer.[25]

Advantages of Theranostics

Once the nanoparticles need to target the tumor cells it should escape from the (i) cell surface binding, (ii) cellular uptake, (iii) move from the lysosomes and (iv)Its relation with sub-cellular location, such as nuclei or mitochondria. They specifically acts by targeting the organelles like mitochondria, endoplasmic reticulum and the to avoid the abnormal changes that results in cancer.[26]

Conventional therapy affects the normal cells resulting in tissue injury. It depends on the dosage and the frequency of drug delivery during chemotherapy. Nanoparticle delivery systems in cancer therapies specifically target the cancerous cells without affecting the normal cells. Nanoparticles are encapsulated to overcome the mechanisms such as rapid proliferation of cells, antigen expression, and leaky tumor vasculature. Nanocarriers can helps in preventing the drug from premature degradation, increases their absorption and pharmacokinetics and helps in good penetration. They also help in anti angiogenesis.[16]

Nanoparticle formulations will overcome the solubility or stability issues for the drug, limitations on route of administration (e.g. breakdown of orally administered drugs), bio-compartmentalization (e.g. blood–brain barrier) or adverse effects of generalized drug administration (e.g. chemotherapy).[27]

Steps to Enhance Tumor Accumulation of Gold Nanoparticles

There are two available methods to enhance the tumour accumulation of gold nanoparticles. One method is that the markers are added to the nanoparticle surface to upgrade the specificity for a nanoparticle and helps to bind it to act as theranostic material in both therapy and diagnostics. The second method uses cells to target the tumor, as larger vehicles may not accumulate at increased rate in non-target organ like the liver. These vehicles would carry the therapeutic nano- particles to the tumor site, and diffuse from the tumor blood vessels into the tumor body. It increases the nanoparticle accumulation in tumour sites and helps in thermal ablation.[28]

Recent advancements in the molecular pathways of disease act a catalyst for the medical diagnostics and therapeutic drug treatment. It assures the gene expression and protein expression and their interactions. The diagnostic therapy can help in guide and monitor therapy based on the interaction of biological and pharmaceuticals with target proteins. In specific protein biomarkers and corresponding tests can be used to predict and monitor drug response. This enables the arrangement of patients into groups that helps to respond to a particular drug treatment regimen with reduced side effects.[29]

II. Future Research

Oral delivery of theranostic nanomedicine will be important field for future research, which will increase the practice of cancer theranostics and enhances the patient's quality of life and make them realize the dream of "chemotherapy at home". Autophagy or auto-phagocytosis is a catabolic process in which intracellular degradation of dysfunctional cellular components or foreign invaders occurs in lysosomes. Autophagy affects nanomedicine after endocytosis and its therapeutic effect by changing intracellular pharmacokinetics of nanomedicine Therefore, autophagy inhibitors loaded in the theranostic nanomedicine can enhance the delivery of diagnostic and therapeutic agents. Thus, advanced nanotheransotics has been under research for diagnosis and therapy of diseases in high efficiency at the cellular and molecular level.[30]

Nanotechnology will revolutionalize in the field of dentistry, healthcare and human life more profoundly than many other developments of the past. Nanotechnology undeniably has a potential to be the most efficient and most favorable form of further diagnosis and management of cancer.[31]

III. Conclusion:

Theranostics has dual function to diagnose the disease and treat it in the peculiar way and open new field of approach in the field of medicine. As like "To do no harm" we should safeguard the patient from the disadvantages of conventional therapy by the upcoming newer technologies.

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